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10/594,455	06/22/2007	Michael Kretschmar	LNK-020	9277

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EXAMINER	
KIM, ALEXANDER D	
ART UNIT	PAPER NUMBER
1656	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/594,455	KRETSCHMAR ET AL.	
	Examiner	Art Unit	
	ALEXANDER D. KIM	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,4-18,20 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2, 4-18, 20 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. In response to the previous Office action, a non-Final rejection (mailed on 01/15/2010), Applicants filed a response and amendment received on 07/15/2010. In said amendment, claims 1, 3, 19 and 21-23 are cancelled, claims 2, 5-8, 12-18 and 20 are amended, and claim 24 is newly added.

Claims 2, 4-18, 20 and 24 are pending in the instant office action and will be examined herein.

Withdrawn-Oath/Declaration

2. The previous objection to the oath or declaration as defective because the claimed foreign priority information is missing, is withdrawn by virtue of applicants' argument.

Withdrawn-Claim Objections

3. The previous objection of Claim 1 (Claims 5-20 and 22-23 dependent therefrom) for reciting "the step of" is withdrawn by virtue of cancelling claim 1.

4. The previous objection of Claims 1, 2, and 22 (Claims 3-20 and 23 dependent therefrom) for reciting abbreviation "VWF" at least once reciting the entire phrase for which the abbreviation is used in its first appearance in the claims; is withdrawn by virtue of applicants' amendment.

5. The previous objection of Claim 2 (Claims 3-4 dependent therefrom) for reciting "The process for purifying VWF comprising the steps of..." wherein it should have been ---A process for purifying VWF comprising steps of ...---; is withdrawn by virtue of applicants' amendment.

6. The previous objection of Claims 3 and 13 for reciting "VWF is found in the flow" (emphasis added), wherein the appropriate term is "flow-through" or "flow through" which is the art recognized terminology; is withdrawn by virtue of applicants' amendment.

7. The previous objection of Claims 22 and 23 because of recitation of "A VWF containing composition... " and "A composition ...", respectively, is withdrawn by virtue of canceling claims 22 and 23.

Claim Objections

8. Claims 2, 4-18, 20 and 24 are objected to because of the following informalities:

Claims 3, 5-7 (Claims 4, 8-18, 20 and 24 dependent therefrom) recite "hydroyapatite". It should be ---hydroxylapatite--- to be consistent through out claims, although both terminology are used and well known in the art.

Appropriate correction is required.

Withdrawn-Claim Rejections - 35 USC § 112

9. The previous rejection of Claim 1 (Claims 5-20 and 22-23 dependent therefrom) under of 35 U.S.C. 112, second paragraph, for reciting "the step of carrying out at lest one hydroxylapatite flow chromatography", wherein the term "the step" lacks antecedent basis, is withdrawn by virtue of cancelling claim 1

10. The previous rejection of claim 5 under of 35 U.S.C. 112, second paragraph, for reciting A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) (i.e., "pH of 6.5 to 8.0", and "preferably 6.8 to 7.5" which is the narrower statement of the range/limitation) is withdrawn by virtue of applicants' amendment.

11. The previous rejection of Claim 6 under of 35 U.S.C. 112, second paragraph, for reciting "the running buffer" which has insufficient antecedent basis for this limitation in the claim, is withdrawn by virtue of applicants' amendment.

Withdrawn-Claim Rejections - 35 USC § 112

12. The previous rejection of Claims 1-20 and 22-23 under 35 U.S.C. § 112, first paragraph, written description, is withdrawn by virtue of applicants' amendment (i.e., limiting to a wild-type VWF); and by virtue of cancelling claims 1, 3, 19 and 22-23.

13. The previous rejection of Claims 1-20 and 22-23 under 35 U.S.C. 112, first

paragraph, scope of enablement, is withdrawn by virtue of applicants' amendment (i.e., limiting to a wild-type VWF); and by virtue of cancelling claims 1, 3, 19 and 22-23.

Withdrawn-Claim Rejections - 35 USC § 102

14. The previous rejection of Claims 1, 3 and 22-23 under 35 U.S.C. 102(b) as being anticipated by Gorman et al. (Thrombosis Research, 1978, Vol. 12, pages 341-352, as cited in IDS), is withdrawn by virtue of cancelling claims 1, 3 and 22-23; and Claims 7-12 are withdrawn by virtue of applicants' amendment (i.e., requiring further step of re-chromatography in hydroxylapatite column from the method steps of claim 2).

15. The previous rejection of Claims 22-23 under 35 U.S.C. 102(b) as being anticipated by Burnouf-Radosevich et al. (Vox Sanguinis, 1992, Vol. 62, pages 1-11, as cited in IDS) is withdrawn by virtue of cancelling claims 1, 3 and 22-23.

16. The previous rejection of Claims 1, 3, 7-12 and 22-23 under 35 U.S.C. 102(b) as being anticipated by Dumas et al. (The Journal of Biological Chemistry, May 28, 2004, Vol. 279, pages 23327-23334) is withdrawn by virtue of cancelling claims 1, 3 and 22-23; and Claims 7-12 are withdrawn by virtue of applicants' amendment (i.e., requiring additional step of re-chromatography in hydroxylapatite from the method steps of claim 2).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. Claims 2, 5-6, 14 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Gorman et al. (Thrombosis Research, 1978, Vol. 12, pages 341-352, as cited in IDS).

The rejection was stated in the previous office action as it applied to previous Claims 1-17, 19 and 22-23. In response to this rejection, applicants have amended Claims 2, 5-8 and 12-17, cancelled Claims 1, 3, 19 and 22-23, and added new claim 24; and traverse the rejection as it applies to the newly amended claims.

Applicants acknowledges that "Gorman et al. teach the step of loading a precipitated and gel-filtered plasma preparation onto a hydroxylapatite column, washing the column with an equilibration buffer and then simultaneously eluting factor VIII and VWF with a gradient from 5mM to 500 mM potassium phosphate buffer (pH 6.8)"; and traverse instant rejection since claim 2 as amended herewith expressly requires the step of carrying out flow chromatography....while VWF is substantially not bound to the hydroxylapatite matrix" and "(ii) collecting a flow through fraction containing unbound VWF" (see bottom of page 9 to top of page 10, Remarks filed on 7/15/2010).

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. According to MPEP 2106[R-5] II, "USPTO

personnel are to give claims their broadest reasonable interpretation in light of the supporting disclosure" but the "Limitations appearing in the specification but not recited in the claims should not be read into the claim". Given the broadest reasonable interpretation of the instant step (i) of claim 2, the recited limitation of "substantially not bound" (emphasis added) includes, but not limited to, a VWF being not bound to the hydroxylapatite matrix; wherein the term "substantially" in the instant claim lacks any degree or any certain amount (10%, 20%..., for example) that is bound and/or unbound. Thus, the instant step (i) includes the step of carrying out hydroxylapatite chromatography for purifying VWF wherein the VWF is bound and/or unbound to the hydroxylapatite resin; in turn, the method of instant claim 2 does not excludes the status of VWF being bound to a hydroxylapatite matrix as taught by Gorman et al. Also, once a VWF is eluted from a hydroxylapatite matrix regardless of previous state (bound to the hydroxylapatite matrix, for example), the eluted VWF becomes "unbound VWF". Thus, given broad and reasonable interpretation of claimed steps, the method taught by Gorman et al. is encompassed by the instant claim 2.

As previously noted, Gorman et al. teach a process of purifying VWF by hydroxylapatite (HA) chromatography. The process of Gorman et al. comprises: precipitation from plasma (an example of purification before the HA column), gel filtration on Sepharoase 6B and HA wherein HA chromatography involves loading, washing with 5mM phosphate (pH 6.8), 0.1 M NaCl; and eluting by 0.1 M phosphate (pH 6.8), 0.1 M NaCl from the gradient of 5 mM to 500 mM potassium phosphate buffer (e.g., washing and/or eluting) which resulted in co-elution having "Factor VIII coagulant

activity, factor VIII related antigen and von Willebrand factor activity" (see the Abstract and the purification procedure on page 342, bottom); thus, the process of Gorman et al. and the co-eluted VWF product thereof meet the limitations of Claims 2, 5-6, 14 and 24.

18. Claims 2 and 5-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Dumas et al. (The Journal of Biological Chemistry, May 28, 2004, Vol. 279, pages 23327-23334).

The rejection was stated in the previous office action as it applied to previous Claims 1-3, 5-17 and 22-23. In response to this rejection, applicants have amended Claims 2, 5-8 and 12-17, cancelled Claims 1, 3 and 22-23; and traverse the rejection as it applies to the newly amended claims.

Applicants argue that Dumas disclosure is similarly deficient as noted above in reference to the teachings of Gorman et al. Applicants further argue that Dumas et al. teach purification of "recombinant VWF fragments". See page 10, lines 4-7, Remarks filed on 7/15/2010.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. For the same reasons above, the instant step (i) of claim 2 includes the step of carrying out hydroxylapatite chromatography for purifying VWF wherein the VWF is bound and/or unbound to the hydroxylapatite resin; in turn, the method of instant claim 2 does not excludes the status of VWF being bound to a hydroxylapatite matrix as taught by Gorman et al. Also, once a VWF is eluted from a hydroxylapatite matrix regardless of previous state (bound to the hydroxylapatite matrix,

for example), the eluted VWF becomes "unbound VWF". Thus, given broad and reasonable interpretation of claimed steps, the method taught by Gorman et al. is encompassed by the instant claim 2 and its dependent claims 5-12 and 24.

Furthermore, the term "wild type VWF" has not been defined in instant specification as to which structure is included or excluded as long as said VWF is identified as wild type, for example. Thus, given broad and reasonable interpretation of recited term "wild type VWF", it encompasses any wild type VWF which includes, but not limited to, the "**wild type** A1 domain of VWF" taught by Dumas et al. as noted in the previous office action mailed on 1/15/2010, page 14, line 7.

"The expression "plasma fraction" refers in this connection to a composition which was obtained from plasma and contains various plasma proteins." according to instant specification on page 11, bottom. Since the instant claim 2 does not require a step of providing a plasma from any animal, for example; in light of instant specification with a broad and reasonable interpretation, the recited term "plasma fraction" is interpreted as any composition containing plasma proteins, wherein said plasma proteins are part of plasma which is encompassed by the meaning of a composition obtained from plasma. Thus, the a solution containing wild type VWF A1 by Dumas et al. is encompassed by the instant plasma fraction.

The solution containing "wild type" A1 domain of VWF (i.e., referred to as the A1) expressed in E. coli by Dumas et al. (see bottom left column, page 23328) meets the limitation of a plasma fraction containing wild-type VWF in Claim **2**.

Dumas et al. teach a process of loading wild type A1 domain of VWF (i.e., referred to as the A1) containing fraction onto hydroxyapatite (HA) column and eluted the A1 by a linear gradient from 20 mM HEPES, pH 8.0 to 20 mM HEPES, 0.5 M sodium phosphate monobasic, 0.5 M sodium phosphate dibasic, pH 6.6; and also teach "purified A1 was judged to be pure (>95%) by SDS-PAGE" which indicating there are about 5% contamination; see page 23328, right column, lines 9-14. Thus, the process of Dumas et al. meets all limitation of **Claims 2 and 5-6**.

Withdrawn-Claim Rejections - 35 USC § 103

19. The previous rejection of Claim 1, 3, 7-13, 19 and 22-23 under 35 U.S.C. 103(a) as being unpatentable over Burnouf-Radosevich et al. or Newman et al. in view of Labrou, Dumas et al. and Zardi et al. is withdrawn by virtue of cancelling claims 1, 3, 19 and 22-23; and by virtue of applicants' amendment in claims 7-13 (i.e., requiring an additional step of HA chromatography from the method of claim 2).

Claim Rejections - 35 USC § 103

20. Claim 2, 4-6, 14-17 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burnouf-Radosevich et al. (Vox Sanguinis, 1992, Vol. 62, pages 1-11, as cited in IDS) or Newman et al. (US Patent 5,710,254, Jan 20, 1998) in view of Labrou (Journal of Chromatography B, 2003, Vol. 790, pages 67-78), Dumas et al. (The Journal of Biological Chemistry, May 28, 2004, Vol. 279, pages 23327-23334), and Zardi et al. (Eur. J. Biochem., 1985, Vol. 146, pages 571-579).

The rejection was stated in the previous office action as it applied to previous Claims 1-17, 19 and 22-23. In response to this rejection, claims 1, 3, 19 and 21-23 are cancelled, claims 2, 5-8, 12-17 are amended, and added new claim 24; and traverse the rejection as it applies to the newly amended claims.

Applicants argue that the instant amendment in claim 2 requiring step of "(i) carrying out flow chromatography with hydroxyapatite by contacting a plasma fraction containing wild-type VWF and one or more contaminating proteins with a hydroxylapatite matrix under conditions that permit at least one contaminating protein to bind to the hydroxylapatite matrix, while VWF is substantially not bound to the hydroxylapatite matrix" and "(ii) collecting a flow through fraction containing unbound VWF". Applicants respectfully submit that none of the prior art references of record disclose or suggest this novel configuration or its resulting improvement. Accordingly, any combination of references will necessarily fail to teach or suggest all the claim limitations and thus cannot be fairly characterized as obviating the invention of the pending claims". See top of page 11, Remarks filed on 7/15/2010. Applicants further argue that instant invention is based on the surprising finding that one can use "flow" or "non binding" HA chromatography, optionally in conjunction with traditional "binding" HA chromatography, to remove a significant portion of undesired proteins from a plasma fraction the thereby yield a VWF of surprisingly high purity (see bottom of page 11 to top of page 12, Remarks filed on 7/15/2010). Applicants argue that Neither Burnouf-Radoservie et al. nor Newman et al. teach a purification method using hydroxylapatite; and Labrou, Dumas, and Zardi do not mentions or suggests VWF, not to mention the

particular utility of non-binding hydroxylapatite chromatography for purifying VWF. Applicants argue that combined teachings of Burnouf-Radosevic or Newman in view of Labrou, Dumas and Zardi would not render obvious the use of non-binding flow hydroxylapatite chromatography for VWF purification (see page 12, middle, Remarks filed on 7/15/2010).

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. Contrary to applicants' argument, it is noted the instant claims are not limited to non-binding HA chromatography because instant claim 2 (and dependent claims thereof) recites "substantially not bound" which includes a binding of VWF to HA column. As similarly noted above, given the broadest and reasonable interpretation in light of instant specification, method step (i) of instant claims 2, 4-6 and 14-17 encompass the step of carrying out hydroxylapatite chromatography for purifying VWF wherein the VWF is bound and/or unbound to the hydroxylapatite resin; in turn, the method of instant claim 2 does not excludes the status of VWF being bound to a hydroxylapatite matrix. Also, once a VWF is eluted from said hydroxylapatite matrix regardless of previous state (bound to the hydroxylapatite matrix, for example), the eluted VWF becomes "unbound VWF". Furthermore, the term "wild type VWF" has not been defined in instant specification as to which structure is included or excluded as long as said VWF is identified as wild type, for example. Thus, given broad and reasonable interpretation of recited term "wild type VWF", it encompasses any wild type VWF which is well known in the art. "The expression "plasma fraction" refers in this connection to a composition which was obtained from plasma and contains

various plasma proteins." according to instant specification on page 11, bottom. Since the instant claim 2 does not require a step of providing a plasma from any animal, for example; in light of instant specification with a broad and reasonable interpretation, the recited term "plasma fraction" can be interpreted as any composition containing plasma proteins, wherein said plasma proteins are part of plasma which is encompassed by the meaning of a composition obtained from plasma.

It is noted the instant rejection is under 35 U.S.C. 103(a) which allows combined teaching of several references as long as there is reasonable expectation of success and motivation to do so as noted in the previous office action. If Burnouf-Radoservic et al. or Newman et al. teach a method of using HA column, it would have been references for rejection under 35 U.S.C. 102(b). According to MPEP 2144 [R-6] I, The rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). See also In re Kotzab, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) (setting forth test for implicit teachings); In re Eli Lilly & Co., 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990) (discussion of reliance on legal precedent); In re Nilssen, 851 F.2d 1401, 1403, 7 USPQ2d 1500, 1502 (Fed. Cir. 1988) (references do not have to explicitly suggest combining teachings); Ex parte Clapp, 227 USPQ 972 (Bd. Pat. App. & Inter. 1985) (examiner must present convincing line of reasoning

supporting rejection); and Ex parte Levengood, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993) (reliance on logic and sound scientific reasoning). The method of using hydroxylapatite column is an established technique for purifying a protein and generally available to one of ordinary skill in the art including VWF which is previously recognized as therapeutically important protein.

Applicants allege "Examiner's comments that Labrou teaches that HA chromatography is "unique in achieving the high standards of product purity dictated by the regulatory authorities for commercial bioproducts" is incorrect as Labrou only states that "chromatography" in general is unique in achieving the high standards of product purity. Thus, when given their proper context and interpretation" (see page 12, lines 13-17, Remarks filed on 7/15/2010. Thus, applicants' argument of Labrou, Dumas, and Zardi are only of limited interest. However, Applicants' argument is incorrect, given their proper context and interpretation; because the Examiner has noted that "Labrou teaches a hydroxyapatite is one of "unique in achieving the high standards of product purity dictated by the regulatory authorities for commercial bio products and a highly selective separation technique commonly used for the isolation and purification of biological macromolecules (see left column, lines 24-35, on page 68)" (with emphasis added), wherein the explicit term "hydroxyapatite" is recited as one of chromatography according to Labrou's teaching (see list of chromatography by Labrou et al., on page 68, line 32). According to MPEP 2144 [R-6] II, The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal

precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Sernaker, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). >See also Dystar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick, 464 F.3d 1356, 1368, 80 USPQ2d 1641, 1651 (Fed. Cir. 2006) ("Indeed, we have repeatedly held that an implicit motivation to combine exists not only when a suggestion may be gleaned from the prior art as a whole, but when the improvement' is technology-independent and the combination of references results in a product or process that is more desirable, for example because it is stronger, cheaper, cleaner, faster, lighter, smaller, more durable, or more efficient. Because the desire to enhance commercial opportunities by improving a product or process is universal—and even common-sensical—we have held that there exists in these situations a motivation to combine prior art references even absent any hint of suggestion in the references themselves.") (emphasis added). Thus, given proper context and interpretation, the teachings of Labrou, Dumas and Zardi provide motivation to use HA chromatography for purifying VWF with a reasonable expectation of success by one skilled in the art and meets all limitation of claimed method step which encompasses step of binding VWF solution in HA matrix and eluting VWF from HA matrix using VWF fraction precipitated by aluminum hydroxide (an example of cryoprecipitation) as starting material before the HA purification and elution of VWF protein from HA column as explicitly taught by Burnouf-Radosevich et al. (see "Starting Material" on page 2, middle of right column).

As similarly noted in the previous office action, Burnouf-Radosevich et al. teach a process of purification of VWF having following steps: cryoprecipitation of plasma by

aluminum hydroxide at a certain pH (an example of a pH precipitation as well as cryoprecipitation), see "Starting Material" on page 2, middle of right column (meeting the limitation of Claims 14-18); and processing steps as shown in Table 1, on page 4; wherein impurities of purified VWF composition contains "traces of fibrinogen ... and fibronectin" in a highly sensitive immunoblotting assay using specific polyclonal antibodies (see last three lines on page 5, right column; meeting the limitations of contaminant protein of Claims 3-4). Burnouf-Radosevich et al. further teach the drawback to using size exclusion chromatography has low protein resolution and lack of stability possible due to protease contamination (see bottom, left column, page 2); thus, affinity column is preferred. Newman et al. also teach "purification of von willebrand factor by affinity chromatography" (see the Title) according to methods disclosed through out the patent; and also teach the presence of "other coagulation factors and other plasma proteins, particularly fibronectin and fibrinogen" is deleterious to the health of the patient (see §, lines 42-46).

Burnouf-Radosevich et al. or Newman et al. **do not** teach a purification method using the hydroxylapatite matrix using Na+ and/or K+ phosphate in a purification buffer.

The use of hydroxylapatite column and the use of Na+ and/or K+ phosphate in a purification buffer (or gradient) for purifying a protein is well known at the time of instant invention as exemplified by the teachings of Labrou, Dumas et al., and Zardi et al. as explained herein.

Labrou teaches a hydroxyapatite is one of "unique in achieving the high standards of product purity dictated by the regulatory authorities for commercial bio

products and a highly selective separation technique commonly used for the isolation and purification of biological macromolecules (see left column, lines 24-35, on page 68). Dumas et al. teach the purification of VWF domains using a hydroxyapatite column and appropriate buffer as set forth above. Zardi et al. also teach the hydroxyapatite chromatography column is useful in resolving and eluting a fibronectin and its domains from human plasma at pH 6.8 (see middle of left column, page 572). Also, the recombinant VWF "biosynthesis in a cell and secretion" is well known by one skilled in the art as disclosed by Newman et al. (US Patent 5,710,254; see § lines 53-60).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the process of purifying VWF by Burnouf-Radosevich et al. by adding a hydroxyapatite chromatography step within the purification process by Burnouf-Radosevich et al. with a reasonable expectation of success because use of any combination of affinity column is well known in the purification of biomolecules which improve a purity or quality in final product of protein of interest (e.g., VWFs). The motivation to do so is provided by Burnouf-Radosevich et al. who teach the usefulness of highly purified VWF for clinical use for treatment of vWF patients (see end of the Abstract). When said VWF is eluded from the HA column, the VWF can be said to an unbound VWF as written in Claim 2. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

21. Claims 18 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burnouf-Radosevich et al. (Vox Sanguinis, 1992, Vol. 62, pages 1-11, as cited in IDS) or Newman et al. (US Patent 5,710,254, Jan 20, 1998) in view of Labrou (Journal of Chromatography B, 2003, Vol. 790, pages 67-78), Dumas et al. (The Journal of Biological Chemistry, May 28, 2004, Vol. 279, pages 23327-23334), and Zardi et al. (Eur. J. Biochem., 1985, Vol. 146, pages 571-579) as applied to claims 2, 4-6, 14-17 and 24 above, and **further in view of** Winkelman (US Patent 4,789,733, Dec. 6, 1988, as cited in the IDS) and Ichitsuka et al. (US Patent 5,441,635, Aug. 15, 1995).

The rejection was stated in the previous office action as it applied to previous Claims 18 and 20 in addition to Claims 1, 3, 7-13, 19 and 22-23. In response to this rejection, claims 1, 3, 19 and 21-23 are cancelled, claims 2, 5-8, 12-18 and 20 are amended, and added new claim 24; and traverse the rejection as it applies to the newly amended claims.

Since applicants have disclosed instant rejection on page 10, Remarks filed on 7/15/2010, it is assumed that applicants have used the same argument above and did not noted any specific argument(s) in terms of references of Winkelman and Ichitsuka et al. as used in supporting references.

Applicants' arguments have been fully considered but are not deemed persuasive for all the reasons stated above. It is noted that references by Winkelman and Ichitsuka et al. are used to address the limitation of claims 18 and 20 as stated herein.

As noted previously (see bottom of page 17 to page 19, non final office action mailed on 1/15/2010), the teachings of Burnouf-Radosevich et al. or Newman et al. in view of Labrou, Dumas et al., and Zardi et al. is disclosed as set forth above. As noted above, Burnouf-Radosevich et al. teach a process of purification of VWF which contains "traces of fibrinogen ... and fibronectin" (see last three lines on page 5, right column).

Burnouf-Radosevich et al. or Newman et al. in view of Labrou, Dumas et al., and Zardi et al. **do not** teach a process of an acidic precipitation (i.e., lowering a pH of buffer, an example of recited "a pH precipitation" in Claim 18) prior to hydroxylapatite chromatography (or fluoroapatite chromatography).

Winkelman et al. discloses that blood plasma fractionation by lowering a pH from 7.0 to 6.0 increase the precipitation of fibronectin and fibrinogen (see §5, lines 60-65).

Ichitsuka et al. disclose the packing material (i.e., fluoroapatite) for liquid chromatography; wherein the fluoroapatite have superior to acid resistance compared to hydroxyapatite (see Example 7, §15, lines 51-52); "proved capable of obtaining a separation pattern similar to that of hydroxyapatite" (see §16, lines 1-2) and "can be used advantageously for separation and purification of proteins, enzymes..." (see Example 8, §16, lines 36-38).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the process of purifying VWF by Burnouf-Radosevich et al. by treating an acidic precipitation of VWF containing loading sample prior to loading to a fluoroapatite column instead of hydroxyapatite with a reasonable expectation of success because said acidic precipitation process and using

a fluoroapatite column instead of hydroxyapatite can be easily performed by one skilled in the art. The motivation to perform an acidic precipitation is provided by Winkelman et al. who teach the usefulness of an acidic precipitation further removes contaminants of fibronectin and/or fibrinogen in the process of VWF purification disclosed by Burnouf-Radosevich et al. because it is advantageous for preparing a higher quality (i.e., higher purity) therapeutic agent; and the motivation to use a fluoroapatite column instead of hydroxyapatite is provided by Ichitsuka et al. who teach a fluoroapatite column has superior stability in an acidic condition which would be created by the precipitation as noted above. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

22. Claims 7-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burnouf-Radosevich et al. (Vox Sanguinis, 1992, Vol. 62, pages 1-11, as cited in IDS) or Newman et al. (US Patent 5,710,254, Jan 20, 1998) in view of Labrou (Journal of Chromatography B, 2003, Vol. 790, pages 67-78), Dumas et al. (The Journal of Biological Chemistry, May 28, 2004, Vol. 279, pages 23327-23334), and Zardi et al. (Eur. J. Biochem., 1985, Vol. 146, pages 571-579) Winkelman (US Patent 4,789,733, Dec. 6, 1988, as cited in the IDS) and Ichitsuka et al. (US Patent 5,441,635, Aug. 15, 1995) as applied to claims 1-20 and 22-23 above, and **further in view of** Daniel Marshak (1996, Cold Spring Harbor Laboratory Press, Strategies for Protein Purification and Characterization: A Laboratory Course Manual) and Schroder et al. (Analytical Biochemistry, 2003, Vol. 313, pages 176-178).

As noted above, Claims 7-13 encompasses an additional step of re-chromatographing the VWF fraction using hydroxylapatite from the eluted VWF from the first HA column chromatography. Thus, instant rejection is focused in case the same hydroxylapatite is used twice.

The rejection was stated in the previous office action as it applied to previous Claim 13 in addition to Claims 1, 3, 7-13, 18-20 and 22-23. In response to this rejection, claims 1, 3, 19 and 21-23 are cancelled, claims 2, 5-8, 12-18 and 20 are amended, and added new claim 24; and traverse the rejection as it applies to the newly amended claims.

Applicants argue that Marshak and Schroder references failed to cure deficiencies of seven other references; and these two references also failed to teach hydroxylapatite chromatography for VWF, much less non-binding HA chromatography for VWF purification since Marshak refers to the purification of calmodulin by DEAE-cellulose chromatography which has no bearing on the obviousness of the present invention. Applicants further argue that instant invention require "conditions where VWF does not bind to the column" (see page 13, line 3, Remarks filed on 7/15/2010). Applicants argue the fact that HA is complicated because it involves both anionic and cationic exchange (see page 13, line 5, Remarks filed on 7/15/2010); and alleges that the instant rejection is improper to arbitrarily pick and choose among disparate reference, cobbling together passages taken out of context to arrive at obviousness and have no reasonable degree of predictability.

Applicants' arguments have been fully considered but are not deemed persuasive for all the reasons stated above. It is noted that instant claim(s) do not recite "conditions where VWF does not bind to the column" but drawn to a condition which "VWF is substantially not bound to the hydroxylapatite matrix" which also encompasses a condition of binding in performing a HA chromatography. references by Winkelman and Ichitsuka et al. are used to address the limitation of claims 18 and 20 as stated herein. As noted above for all reasons stated above, non of previous references do not failed to teach claimed method steps. As noted previously, Schroder et al. teach well known hydroxyapatite chromatography which "involves both anionic and cationic exchange" (see right column, lines 11-12) and "the phosphate concentration required to elute any protein can be reduced by raising the pH" (emphasis added; i.e., binding is weaker at higher pH; see right column, lines 24-25); thus, teaches a specific conditions which can be manipulated by one skilled in the art with a reasonable expectation of success. Although Daniel Marshak teaches "It is not uncommon to see published protocol that calls for two or three successive DEAE-cellulose columns" and "It is not bad to use two anion- or cation-exchange steps at very different pH" (see page 58, lines 29-31 and lines 37-38). However, because a protein purification through column chromatography techniques are so well known, and given the common mechanism of binding in a column matrix (which involves cation and/or anion); the use of same column multiple time at different condition (pH for example) is only limited to DEAE is out of context of combined teachings by references of Marshak and Schroder by one skilled in the art for VWF purification. Because hydroxylapatite chromatography is so well known

in a protein purification, specifically including purification of VWF, the rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles that some advantage or expected beneficial result would have been produced by their combination as noted herein within the context of all references above. Thus, instant rejection is proper in light of reasonable expectation of success and motivation provided previously and herein.

As similarly noted in the previous office action (mailed on 1/15/2010, pages 19-21), the teachings of Burnouf-Radosevich et al. or Newman et al. in view of Labrou, Dumas et al., Zardi et al. Winkelman and Ichitsuka et al. is disclosed as set forth above.

Burnouf-Radosevich et al. or Newman et al. in view of Labrou, Dumas et al., Zardi et al. Winkelman and Ichitsuka et al. **do not** teach a process of running VWR fraction on a hydroxylapatite chromatograph under non-binding conditions and re-chromatograph said VWR fraction on a hydroxylapatite again second time.

Daniel Marshak teaches "It is not uncommon to see published protocol that calls for two or three successive DEAE-cellulose columns" and "It is not bad to use two anion- or cation-exchange steps at very different pH" (see page 58, lines 29-31 and lines 37-38).

Schroder et al. teach the hydroxyapatite "involves both anionic and cationic exchange" (see right column, lines 11-12) and "the phosphate concentration required to elute any protein can be reduced by raising the pH" (emphasis added; i.e., binding is weaker at higher pH; see right column, lines 24-25).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the process of purifying VWF by incorporating a step of using hydroxylapatite multiple times wherein the VWF would be present in the flow-through in one time and the VWF would be bound to hydroxylapatite and eluted by the phosphate ions by adjusting or optimizing the pH of buffer and loading sample because manipulation and/or optimization of a column chromatography protein purification scheme is readily performed by one skilled in the art. The motivation to do so is well known by one skilled in the art who has desired to obtain more pure VWF final product which is advantageous for preparing a higher quality (i.e., higher purity) therapeutic VWF agent. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

The buffer used in HA column is well known such as "linear gradient of 0.5-190 mM sodium phosphate buffer (pH 6.8)" (see Zardi et al., middle, left column, page 572; meeting limitations of claims 9-10, 12). As noted above, Dumas et al. teach a process of purifying wild type A1 domain of VWF (i.e., referred to as the A1 which is encompassed by instant wild type VWF because instant specification does not define the term "wild type VWF" and instant claims do not have structural limitation nor functional limitations; as long as it is a wild type of VWF polypeptide) containing fraction onto hydroxyapatite (HA) column and eluted the A1 by a linear gradient from 20 mM HEPES, pH 8.0 to 20 mM HEPES, 0.5 M sodium phosphate monobasic, 0.5 M sodium phosphate dibasic, pH 6.6 (meeting limitation of instant claim 11, see page 23328, right column, lines 9-14).

Withdrawn-Double Patenting

23. The previous rejection of Claims 1-20 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 4-6, 8-17 and 26-27 of U.S. Patent No: to be issued, from the US Patent Application 10/594,454 (now US patent 7659247), wherein the applicants have paid issue fee on 12/18/2009), is withdrawn by virtue of cancelling claims 1, 3 and 19; and the terminal disclaimer filed on 9/29/2009 in US Patent Application 10/594,454 (now US patent 7659247).

24. The previous rejection of Claims 1 and 3 provisionally rejected on the ground of nonstatutory double patenting over claims 2, 4-15, 17 and 24 of U. S. Patent Application No. 10/594,453, is withdrawn by virtue of cancelling claims 1 and 3.

Double Patenting

25. Claims 2, 4-18 and 24 are provisionally rejected on the ground of nonstatutory double patenting over claims 2, 4-15, 17 and 24 of U. S. Patent Application No. 10/594,453 since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.

The rejection was stated in the previous office action as it applied to previous Claims 1-18. In response to this rejection, applicants have amended Claims 2, 5-8, 12-18, cancelled Claims 1, 3, 19, and claim 24 is newly added.

Applicants will consider the submission of terminal disclaimer; and which to hold in abeyance such a filing (see bottom of page 13, Remarks filed on 7/15/2010); thus, instant rejection is maintained.

As noted previously, the subject matter claimed in the instant application is fully disclosed in the US patent application and the application are claiming common subject matter, as follows: Instant claims 1-18 are anticipated and/or obvious by Claims 2, 4-15, 17 and 24 from US Patent Application No. 10/594,453 [i.e., species of instant claimed process by further limiting limitation(s); wherein Claim 17 specifically recites the coagulation factor is **von Willebrand factor** which is encompassed by its independent claim 2 (i.e., having a pH precipitation as shown by the instant Claim 18) and all of its dependent claims 4-6, 8-15, 17 and 24], in view of the specification of US Patent Application No. 10/594,453 as explained below. It is noted that the certified translation of foreign priority application is the specification in US Patent application 10/594,**454**; and another related application 10/594,453 do not have specification filed in the application. Thus, for the examination purpose, the certified translation of foreign priority application in US Patent application 10/594,453 is treated as the specification (although it was filed and labeled as FRPR, see FRPR filed on 9/26/2006 having 18 pages). The specification of US Patent Application No. 10/594,453 discloses separating unbound VWF from hydroxyapatite while fibronectin is bound to hydroxyapatite (see page 7, top; instant Claims 3-4); discloses carrying out hydroxyapatite chromatography at pH 7.0-7.5 (for example, see page 7, line 17, instant claims 5 and 12); discloses the process of instant Claims 6 and 8-11 (see bottom of page 8 to top of page 9); discloses

the process of instant Claims 7 and 13 (see bottom of page 10 to top of page 11); discloses the process of instant Claims 14-17 (see page 4, lines 1-4).

More specifically, the process of Claims 4-5 and 9 of US Patent Application No. 10/594,453 anticipate instant Claim 9. The process of Claims 14-15 of US Patent Application No. 10/594,453 anticipate instant Claims 15-17.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

26. Claims 2, 4-18, 20 and 24 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered section in this Office action to be fully responsive in prosecution.

Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALEXANDER D. KIM whose telephone number is (571)272-5266. The examiner can normally be reached on 10AM-6:30PM.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Alexander D Kim/
Examiner, Art Unit 1656